

## **REMARKS**

### **I. Status of the Application**

Claims 1-4, 6, 8-23, 25-30, 32, 34-45, 47-51 are presently pending and stand rejected. By way of this response, sixteen (16) claims have been amended and eleven (11) claims have been cancelled. Applicant respectfully submits that no new matter has been added by way of this amendment.

Support for the amendment to claim 1 can be found at least in paragraphs [0045]-[0052] of the application as published (US 2006/0211664).

Claim 6 has been amended for clarification purposes.

Support for the amendment to claims 9 and 12 can be found at least in paragraph [0093] of the application as published (US 2006/0211664).

Claim 19 has been amended to change claim dependency.

Claim 20 has been amended for grammatical purposes.

Support for the amendment to claim 21 can be found at least in paragraph [0041] of the application as published (US 2006/0211664).

Support for the amendment to claim 23 can be found at least in paragraph [0050] of the application as published (US 2006/0211664).

Support for the amendment to claims 25 and 27 can be found at least in paragraphs [0045]-[0052] of the application as published (US 2006/0211664).

Claim 32 has been amended for clarification purposes.

Claim 41 has been amended to change claim dependency.

Claim 42 has been amended for grammatical purposes.

Support for the amendment to claim 43 can be found at least in paragraph [0041] of the application as published (US 2006/0211664).

Support for the amendment to claim 45 can be found at least in paragraph [0050] of the application as published (US 2006/0211664).

Support for the amendment to claim 47 can be found at least in paragraph [0045]-[0052] of the application as published (US 2006/0211664).

## **II. CLAIMS 9 AND 50, AS AMENDED, COMPLY WITH 35 U.S.C. § 112, PARA. 2.**

In the Office Action, the Examiner rejected claims 9 and 50 under 35 U.S.C. § 112, para. 2, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, “[c]laims 9 and 50 contain the trademark/trade name MY 5445. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirement of 35 U.S.C 112, second paragraph.” *See* Office Action, at 2-3. Without admitting or conceding in any manner that claims 9 and 50 are indefinite, and solely to expedite the prosecution of the present application, claim 9 has been amended to recite the chemical name and claim 50 has been cancelled.

Applicant respectfully submits that the rejection is now moot in view of the present amendment to claims 9 and 50, and requests withdrawal of the rejection under 35 U.S.C. § 112, para. 2.

## **III. DOUBLE PATENTING REJECTION.**

Claims 1-4, 6, 8-23, 25-30, 32, 34-45 and 47-51 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-7, 10-16, 18-23, 25-27, 30-33, 35-38, 40-45, and 47-48 of copending U.S. Patent Appl. No. 10/867,435. Applicant will submit a terminal disclaimer once allowable subject matter is indicated.

## **IV. THE REFERENCES COMBINED IN THE OFFICE ACTION DO NOT RENDER ANY OF THE PENDING CLAIMS UNPATENTABLE UNDER 35 U.S.C. § 103(a).**

Claims 1-4, 6, 8-23, 25-30, 32, 34-45 and 47-51 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,730,987 (“Omar”), WO 99/24041 (“Mak”) and WO 93/25168 (“Heiber”) in view of WO 96/27372 (“Allen”) and US 6,200,591 (“Hussain”). Applicant respectfully traverses the rejection and respectfully requests that the rejection be withdrawn in light of the arguments set forth below and the present amendments to the claims.

### **A. Legal Standards for Nonobviousness under 35 U.S.C. § 103(a)**

The burden of establishing a *prima facie* case of obviousness lies with the Office. To establish a *prima facie* case of obviousness, a number of basic criteria must be met. M.P.E.P. §

2143. First, there must be some apparent reason, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418, 82 U.S.P.Q.2d 1385 (2007). Second, there must be a reasonable expectation of success. *Id.* at 421. Third, the references when combined must teach or suggest all the claim limitations. *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1351, 89 U.S.P.Q.2d 1161 (Fed. Cir. 2008); *Ex Parte H. Garrett Wada, and Matthew B. Murphy*, Appeal No. 2007-3733, 2008 WL 142652, at \*4 (B.P.A.I. January 14, 2008). Furthermore, the determination of obviousness is made with respect to the subject matter as a whole. *KSR*, 550 U.S. at 406; 35 U.S.C. § 103(a); M.P.E.P. § 2141.02.

As will be discussed in detail below, Applicant submits that a *prima facie* case of obviousness has not been established because (i) the references, alone or as a whole, do not disclose each and every element of the claimed invention, (ii) there was no apparent reason to combine the cited references, and (iii) there was not a reasonable expectation of success.

**B. The Cited References, Alone or Combined, Fail to Create a *prima facie* Case of Obviousness.**

**1. The combined references, alone or as a whole fail to teach all the claim limitations.**

To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested in the prior art references. M.P.E.P. § 2143. In this case, the references, alone or as a whole, do not teach or suggest all the claim limitations of the pending application. The combination of cited references as a whole fail to teach, explicitly or inherently, all of the claim limitations, including (1) the testosterone gel composition comprising, *inter alia*, isopropyl myristate, and (2) the use of a phosphodiesterase inhibitor or a pharmaceutical agent for treating erectile dysfunction in combination with testosterone for improving sexual performance.

In particular, Omar teaches a composition comprising a mixture of lyophilized roe and a dry powered extract from leaves of *Ginkgo biloba* for treating impotence in human males. *See* col. 3, line 14-19; col. 4, lines 27-39. Further, Omar teaches that the composition may be used in combination with testosterone. *See* claim 8. However, Omar does not teach or suggest a method of improving sexual performance in a subject in need thereof comprising the pending pharmaceutical testosterone composition in combination with a phosphodiesterase inhibitor or a pharmaceutical agent for treating erectile dysfunction. In fact, Omar does not even teach or

suggest the pharmaceutical testosterone composition or any of the recited phosphodiesterase inhibitors or pharmaceutical agents, let alone the combination thereof. Rather, Omar emphasizes the synergistic effect of ginkgo biloba extract and lyophilized roe and the benefits thereof.

Mak teaches a composition having a penetration-enhancing system that includes oleic acid. *See* col. 4, lines 9-32. The composition also comprises an active agent, a C<sub>1</sub>-C<sub>4</sub> alcohol and a glycol, and optionally a gelling agent, preferably polyacrylic acid. *See* page 3, lines 1-4. In contrast, the instant invention contains isopropyl myristate as the sole penetration enhancer. Mak clearly does not disclose a composition without oleic acid.

Heiber discloses a transdermal/transmucosal drug delivery system that contains glycerin, which acts as a permeation flux moderator, and helps maintain a relatively uniform dosing profile. *See* page 4, lines 21-25. The problem addressed by Heiber was “burst effect,” which Heiber describes as, “[the delivery system] may deliver a very high dose of the drug initially which then drops or levels off after a period of time to reach acceptable levels.” *Id.*, at page 3, lines 16-23. Heiber does not teach or suggest a method of improving sexual performance in a subject in need thereof comprising the instant pharmaceutical testosterone composition in combination with a phosphodiesterase inhibitor or a pharmaceutical agent for treating erectile dysfunction. The testosterone composition in Example 3 of Heiber does not even contain a penetration enhancer. In fact, Heiber teaches that a penetration enhancer is optional. *Id.*, at pg. 4, lines 30-34; pg. 9, lines 20-24; Example 3. Rather, Heiber highlights the use of glycerin as a moderator of “burst effect” in a transdermal drug delivery system.

Allen teaches a stable, uniform, water-based topical cream containing nitroglycerin for treating a male patient suffering from erectile dysfunction. The topical cream comprises nitroglycerin, a penetration enhancer, water, thickener, and an emulsifier. Allen does not teach or suggest any of the phosphodiesterase inhibitors or pharmaceutical agents for improving sexual performance or their use in combination with the pending pharmaceutical composition.

Hussain discloses a novel intranasal delivery of sildenafil. Hussain teaches that the invention may be used in combination with other drugs used in the treatment of erectile dysfunction. However, Hussain does not teach or suggest the pending pharmaceutical testosterone composition or of any of the recited phosphodiesterase inhibitors or pharmaceutical agents for treating erectile dysfunction.

Based upon the foregoing, it is clear that the cited references as a whole do not suggest or disclose all of the claim limitations of the present invention. Consequently, Applicant respectfully requests withdrawal of the rejection under § 103(a).

## **2. No apparent reason to combine the cited references**

Further, even if each and every claim limitation in the presently amended claims were disclosed in the cited prior references, which is not admitted herein, Applicant respectfully submits that no apparent reason exists to combine the references as suggested in the July 9, 2009 Office Action. In *KSR Int'l Co. v. Teleflex Inc.*, 550 US 398; 82 U.S.P.Q.2d 1385 (2007), the United States Supreme Court affirmed that in order for references to be combined to form the basis of an obviousness rejection, it is “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way that claimed new invention does.” *Id.* at 418. Moreover, under *KSR*, a claim is “not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *Id.* To establish a *prima facie* case of obviousness when combining multiple references, there must be an “explicit” analysis of both the claimed invention and the prior art to determine “whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.” *Id.* Indeed, the M.P.E.P. specifically states that “[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.” M.P.E.P. § 2143.01 (emphasis in original).

Applying this settled rule, the Office Action has failed to meet the standards set forth in *KSR* to identify any reason why a person of ordinary skill in the art at the time of the invention would have combined the prior art references to obtain the claimed invention. The references cited specifically emphasize the advantages of their disclosed formulation, such that one of skill in the art would not be motivated to venture outside the formulations provided therein. Specifically, Omar teach the synergistic effect of the mixture of ginkgo biloba extract and lyophilized roe in treating impotence. One of skill in the art at the time of the invention would not be motivated to combine Omar with any of the cited references because any other combination would not necessarily result in the same synergism.

Likewise, Mak teaches a composition having a penetration-enhancing system that must include oleic acid. Again, a skilled artisan at the time of the invention would not reasonably

substitute oleic acid with isopropyl myristate due to advantages of oleic acid as a penetration enhancer:

“Before the advent of the present invention, it was believed that oleic acid, oleyl alcohol and esters of oleic acid were all equal in their ability to enhance penetration and reduce skin irritation. Surprisingly, it has been discovered that oleic acid is far superior to oleyl alcohol in its ability to reduce skin irritation. This is especially true when oleic acid is used in combination with a gelling agent.” Mak *et al.* at page 5, lines 26-30

Further, the specification in Mak states that oleic acid “not only maintains the [penetration enhancing] system’s ability to enhance topical and transdermal drug delivery, but produces the unanticipated result of reduced skin irritation.” See page 10, lines 16-19. In contrast, the present invention does not contain any oleic acid, but employs isopropyl myristate as the penetration enhancer. One of skill in the art would have no apparent reason to substitute isopropyl myristate in place of oleic acid, since Mak clearly teaches the superiority of oleic acid in the composition. Moreover, none of the other cited references combined with Mak would suggest or motivate a skilled person to make this substitution.

Heiber discloses the use of glycerin to moderate the “burst effect” of transdermal drug delivery systems. One of skill in the art would not be motivated to remove glycerin from a testosterone transdermal formulation, since Heiber teaches that testosterone “exhibits a very high initial burst effect which would not be beneficial to any known form of treatment of a testosterone deficiency.” See pg. 19, lines 11-18. In fact, Heiber teaches away from a transdermal testosterone formulation that does not contain glycerin.

Lastly, Allen admonishes the “judicious selection of ingredients” to formulate a drug delivery penetration enhancing system that is faster acting and improves “feel”. Allen teaches that “[t]he results and properties achieved by the present invention are due to the ***judicious selection*** of the ingredients and their relative amounts. (emphasis added).” See page 7, lines 18-26. This “judicious selection of the ingredient” does not include the presently pending pharmaceutical testosterone composition. Moreover, the drug delivery penetration enhancing system cannot simply be employed with testosterone and expect the same desired results and properties disclosed in Allen, since Allen teaches a *judicious selection* in the formulation.

Clearly, a skilled artisan would be dissuaded from changing the formulation for fear of losing the benefits disclosed therein. Based on the foregoing, Applicant respectfully submits that one of skill in the art would have no apparent reason to combine the cited references.

### 3. No expectation of success in combining the references

As briefly set forth above, a *prima facie* case of obviousness requires that a person of ordinary skill in the art have a reasonable expectation of success regarding the suggested combination of references. *Noelle v. Lederman*, 355 F.3d 1343, 1351-52 (Fed. Cir. 2004), 69 U.S.P.Q.2d 1508; MPEP § 2143.02. Moreover, the reasonable expectation of success must be found in the cited references and not in Applicant's disclosure. *Id.*

One of skill in the art at the time of the invention would have no expectation of success in combining the cited references because each of the references is directed toward a specific problem and the resolution thereof. For example, Mak is directed toward formulations that allegedly exhibit lower levels of irritation than other products, in particular, the use of oleic acid and not isopropyl myristate. Even if an oleic-free and/or a glycol-free penetration enhancing system would be contrivable, which is not admitted herein, Applicant respectfully submits that there is no expectation of success that such a system would perform at least as comparable as Mak. One of ordinary skill in the art would not necessarily expect the same results using isopropyl myristate because as stated in Remington: The Science and Practice of Pharmacy (20th Ed., 2000) at p. 842:

“Even though *in vitro* studies of percutaneous transport may reflect the resistance of the skin to drug diffusion, **there is no way such studies can characterize adequately** the transfer of diffusing drug into the microvasculature of the dermis and its subsequent transfer into general circulation.”

Based on this admonition, one skilled in the art would not reasonably expect the same enhanced delivery and reduce skin irritation using isopropyl myristate. Indeed, penetration enhancers are known to have varied efficacy and skin irritation.

Heiber teaches the use of glycerin to moderate the “burst effect” of transdermal drug delivery systems. As explained *supra*, Heiber teaches that transdermal testosterone exhibits a very high initial burst effect which would not be beneficial to any known form of treatment of a testosterone deficiency, and thus the novel utilization of glycerin to moderate the burst effect.

Therefore, one skilled in the art would have no reasonable expectation of success in combining the references to obtain a formulation that does not contain glycerin. Lastly, Allen prescribes the “judicious selection of ingredient” in the formulation of a penetration enhancing system. Notably, the ingredients are different from that of the pending pharmaceutical composition. Based on this “judicious selection of ingredient,” one skilled in the art would have no reasonable expectation of success in substituting testosterone in place of nitroglycerin. Further, nitroglycerin and testosterone have different modes of action; namely nitroglycerin acts locally at the situs of administration, while testosterone enters the bloodstream to achieve hormonal steady state levels.

In light of the teachings of the aforementioned references, there would be no expectation of success in any composition entirely devoid of these teachings, as is the case of the pending pharmaceutical composition. Indeed, one of skill in the art would have had to ignore these references to obtain the present invention. Thus, a person of ordinary skill in the art would not have had a reasonable expectation of success in combining these reference to obtain the present invention. For at least the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness. Therefore, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 103(a).



## CONCLUSION

For at least the foregoing reasons, it is respectfully submitted that amended claims are in condition for allowance. Early and favorable consideration is respectfully requested, and the Examiner is encouraged to contact the undersigned with any questions or to otherwise expedite prosecution. Further, none of Applicant's amendments or cancellations are to be construed as dedicating any such subject matter to the public, and Applicant reserves all rights to pursue any such subject matter in this or a related patent application.

Respectfully submitted,

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